

(4) Conditions and any limitations that FDA deems necessary regarding use of the drug.

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§516.161 Modifications to indexed drugs.

(a) After a drug is listed in the index, certain modifications to the index listing may be requested. Any modification of an index listing may not cause an indexed drug to be a different drug (or different combination of drugs) or a different dosage form. If such modification is requested, FDA will notify the holder that a new index listing is required for the new drug or dosage form.

(b) Modifications to the indexed drug will fall under one of three categories and must be submitted as follows:

(1) *Urgent changes.* (i) The following modifications to an indexed drug or its labeling should be made as soon as possible, and a request to modify the indexed drug should be concurrently submitted:

(A) The addition to package labeling, promotional labeling, or prescription drug advertising of additional warning, contraindication, side effect, or cautionary information.

(B) The deletion from package labeling, promotional labeling, and drug advertising of false, misleading, or unsupported indications for use or claims for effectiveness.

(C) Changes in manufacturing methods or controls required to correct product or manufacturing defects that may result in serious adverse drug events.

(ii) The modifications described in paragraph (b)(1)(i) of this section must be submitted to the Director, OMUMS, in the form of a request for modification of an indexed drug, and must contain sufficient information to permit FDA to determine the need for the modification and whether the modification appropriately addresses the need.

(iii) FDA will take no action against an indexed drug or index holder solely because modifications of the kinds described in paragraph (b)(1)(i) of this section are placed into effect by the holder prior to receipt of a written no-

tice granting the request if all the following conditions are met:

(A) A request to modify the indexed drug providing a full explanation of the basis for the modifications has been submitted, plainly marked on the mailing cover and on the request as follows: "Special indexing request—modifications being effected;"

(B) The holder specifically informs FDA of the date on which such modifications are to be effected and submits two printed copies of any revised labeling to be placed in use, and

(C) All promotional labeling and all drug advertising are promptly revised consistent with modifications made in the labeling on or within the indexed drug package.

(2) *Significant changes.* (i) The following modifications to an indexed drug or its labeling may be made only after a request has been submitted to and subsequently granted by FDA:

(A) Addition of an intended use.

(B) Addition of a species.

(C) Addition or alteration of an active ingredient.

(D) Alteration of the concentration of an active ingredient.

(E) Alteration of dose or dosage regimen.

(F) Alteration of prescription or over-the-counter status.

(ii) Each modification described in paragraph (b)(2)(i) of this section must go through the same review process as an original index listing and is subject to the same standards for review.

(iii) Each submission of a request for a modification described in paragraph (b)(2)(i) of this section should contain only one type of modification unless one modification is actually necessitated by another, such as a modification of dose necessitated by a modification of the concentration of an active ingredient. Submissions relating to addition of an intended use for an existing species or addition of a species should be submitted separately, but each such submission may include multiple additional intended uses and/or multiple additional species.

(3) *Minor changes.* All modifications other than those described in paragraphs (b)(1) and (b)(2) of this section including, but not limited to, formulation, labeling, and manufacturing

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methods and controls (at the same level of detail that these were described in the request for determination of eligibility for indexing) must be submitted as part of the annual indexed drug experience report or as otherwise required by §516.165.

(c) When changes affect the index listing, it will be updated accordingly.

§516.163 Change in ownership of an index file.

(a) A holder may transfer ownership of a drug's index file to another person.

(1) The former owner shall submit in writing to FDA a statement that all rights in the index file have been transferred, giving the name and address of the new owner and the date of the transfer. The former owner shall also certify that a complete copy of the following, to the extent that they exist at the time of the transfer of ownership, has been provided to the new owner:

(i) The request for determination of eligibility;

(ii) The request for addition to the index;

(iii) Any modifications to the index listing;

(iv) Any records and reports under §516.165; and

(v) All correspondence with FDA relevant to the indexed drug and its index listing.

(2) The new owner shall submit the following information in writing to FDA:

(i) The date that the change in ownership is effective;

(ii) A statement that the new owner has a complete copy of all documents listed in paragraph (a)(1) of this section to the extent that they exist at the time of the transfer of ownership;

(iii) A statement that the new owner understands and accepts the responsibilities of a holder of an indexed drug;

(iv) The name and address of a new primary contact person or permanent-resident U.S. agent; and

(v) A list of labeling changes associated with the change of ownership (e.g., a new trade name) as draft labeling, with complete final printed labeling to be submitted in the indexed drug annual report in accordance with §§516.161 and 516.165.

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(b) Upon receiving the necessary information to support a change of ownership of a drug's index file, FDA will update its publicly-available listing in accordance with §516.157.

§516.165 Records and reports.

(a) *Scope and purpose.* (1) The record-keeping and reporting requirements of this section apply to all holders of indexed drugs, including indexed drugs intended for use in medicated feeds.

(2) A holder is not required to report information under this section if the holder has reported the same information under §514.80 of this chapter.

(3) The records and reports referred to in this section are in addition to those required by the current good manufacturing practice regulations in parts 211, 225, and 226 of this chapter.

(4) FDA will review the records and reports required in this section to determine, or facilitate a determination, whether there may be grounds for removing a drug from the index under section 572(f) of the act.

(b) *Recordkeeping requirements.* (1) Each holder of an indexed drug must establish and maintain complete files containing full records of all information pertinent to the safety or effectiveness of the indexed drug. Such records must include information from foreign and domestic sources.

(2) The holder must, upon request from any authorized FDA officer or employee, at all reasonable times, permit such officer or employee to have access to copy and to verify all such records.

(c) *Reporting requirements.* (1) *Three-day indexed drug field alert report.* The holder must inform the appropriate FDA District Office or local FDA resident post of any product or manufacturing defects that may result in serious adverse drug events within 3 working days of first becoming aware that such a defect may exist. The holder may initially provide this information by telephone or other electronic communication means, with prompt written followup. The mailing cover must be plainly marked "3-Day Indexed Drug Field Alert Report."

(2) *Fifteen-day indexed drug alert report.* The holder must submit a report on each serious, unexpected adverse